

## **REMARKS**

### **Status of the Claims**

Reconsideration of the application is respectfully requested. Claims 1-2, 4-13, and 15-25 are pending. Claims 1, 4, 6, 12-13, 15, 24, and 25 have been amended. Claim 14 remains withdrawn from consideration.

Claim 1 has been amended to recite a method of inducing homologous recombination rather than a method of increasing homologous recombination, and that the homologous recombination occurs at a genetic locus in a eukaryotic somatic cell. Support for this amendment may be found, for example, in U.S. Patent Application Publication No. 2006/0099678 (hereafter “the ‘678 Publication”), which is the publication of the application as filed, in [0010] where it states that “the present invention has the objective of providing a method for *inducing* somatic cell homologous recombination at a genetic locus in a somatic cell” (emphasis added). Additional support for this amendment to claim 1 may be found, for example, in [0011], [0014], [0015], and [0017] of the ‘678 Publication. Claim 1 has also been amended to clarify that homologous recombination is induced by controlling transcription of the gene using a transcription promoter that is located 3’ to the DNA sequence, and the gene is located 3’ to the transcription promoter. Support for this amendment may be found, for example, in [0015], [0053], and [0071] of the ‘678 Publication. Lastly, in amended claim 1, the phrase “wherein the DNA sequence is upstream on the 5’ side of the gene” has been deleted because it is no longer necessary for understanding, in view of the other amendments to claim 1 as discussed above, that the DNA sequence, the transcription promoter, and the gene are arranged in an order beginning with the DNA sequence, the transcription promoter that is located 3’ to the DNA sequence, and the gene is located 3’ to the transcription promoter.

Claim 4 has been amended to clarify that the gene of the method is under transcriptional control by a cis-acting region. Support for this amendment may be found, for example, in [0042] on page 3 of the ‘678 Publication. Claim 5 has been amended to delete the phrase “wherein the transcription promoter is capable of controlling the gene” because the phrase is unnecessary since

claim 5 depends from claim 1. Claim 5 has also been amended to specify that on the vector the DNA sequence, the transcription promoter, and the gene are arranged in order beginning with the DNA sequence, the transcription promoter 3' to the DNA sequence, and the gene 3' to the transcription promoter. Support for the second amendment to claim 5 may be found, for example, in [0045] of the '678 Publication. Claim 6 has been amended for greater clarity by adding the phrase "vector includes an" at the beginning of the phrase starting with the word "wherein". The amendment of claim 6 clarifies that the vector includes an enhancer or a nuclear matrix attachment region (MAR), or both. Support for this amendment may be found, for example, in [0040] – [0044] on page 3 of the '678 Publication.

Claim 10 has been amended for consistency with amended claim 1, from which it indirectly depends, by deletion of the phrase "comprising a base sequence similar to the gene". Support for this amendment may be found, for example, in [0014] and [0015] of the '678 Publication. Claim 12 has been amended to specify that homologous recombination in a cell has been "induced" rather than "enhanced". Support for this amendment may be found, for example, in [0010] on page 1 of the '678 Publication. Claim 13 has been amended to specify a recombinant gene produced by homologous recombination "induced" according to the method of claim 1 rather than "increased" by homologous recombination. Support for this amendment may be found, for example, in [0015] on page 1 of the '678 Publication.

Claim 15 has been amended to clarify that on the vector the DNA sequence, the promoter, and the gene are arranged in an order beginning with the DNA sequence, the transcription promoter 3' to the DNA sequence, and the gene 3' to the transcription promoter. Support for this amendment may be found, for example, in Figure 1, [0013], [0021], [0022] – [0025], [0053], and [0071] of the '678 Publication. Claim 16 has been amended to clarify that the enhancer is located 3' or 5' of the gene and the nuclear matrix attachment region (MAR) is located 3' or 5' to the gene. Additionally, claim 16 has been amended to recite that if the vector contains both an enhancer and a MAR, the enhancer is located 3' or 5' to the gene and the MAR is located 3' or 5' to the enhancer. Support for the amendments to claim 16 may be found for, example, in [0027] of the '678 Publication. Claim 20 has been amended for consistency with amended claim 1 by deletion of the phrase

“similar to the gene”. Support for this amendment may be found, for example, in [0014] and [0015] of the ‘678 Publication. Each of claims 24 and 25 has been amended to recite that homologous recombination has been “induced” rather than “increased” in a cell. Support for this amendment may be found, for example, in [0010] on page 1 of the ‘678 Publication.

No new matter has been added.

**Rejection under 35 U.S.C. § 112, First Paragraph – New Matter**

Claims 1, 2, 4-13, and 15-25 stand rejected as failing to comply with the written description requirement. The Examiner states the phrases: “a method of increasing homologous recombination (claim 1); “recombination has been enhanced” (claim 12); “a recombinant gene produced by increased . . .” (claim 13); and “homologous recombination has been increased” (in each of claims 24 and 25) constitute new matter.

Claims 1, 12-13, 24, and 25 have been amended to recite a form of the verb “induce” rather than a form of the verb “increase” or “enhance”. As discussed in the foregoing comments, these amendments find support in the application as filed, and do not constitute new matter. Specifically, the phrases indicating induction of homologous recombination are found throughout the specification, not only in the passages exemplified above. Claims 2, 4-11, and 17-23 depend directly or indirectly from claim 1, and further specify features of claim 1 that find support in the application as filed.

With respect to independent claim 15, and claim 16 that depends from it, the Examiner has not provided any reason why the subject matter of these claims constitutes new matter. It is assumed that the reason is the same as for claim 1.

Amended claim 15 is directed to a vector of inducing homologous recombination and requires that on the vector the DNA sequence, the promoter, and the gene are arranged in an order beginning with the DNA sequence, the transcription promoter at the 3’ end of the DNA sequence, and the gene at the 3’ end of the transcription promoter. The amendments to claim 15 do not constitute new matter because the subject matter finds support, for example, in Figure 1 of the ‘678

Publication that depicts that on the vector the DNA sequence (*i.e.*, the enhanced green fluorescent protein (EGFP) sequence), the promoter (*i.e.*, the tetracycline inducible promoter (TRE)), and the gene (*i.e.*, enhanced cyan fluorescent protein (ECFP) gene) are arranged in an order beginning with the EGFP sequence, the TRE transcription promoter at the 3' end of the EGFP sequence, and the ECFP gene at the 3' end of the TRE transcription promoter. Amended claim 15 also finds support, for example, in [0013], [0021], [0022] – [0025], [0053], and [0071] of the '678 Publication. As discussed in the foregoing comments, amended claim 16 now recites the location on the vector of the enhancer and/or the MAR relative to the location of the gene, and is supported in [0027] of the '678 Publication. Thus, amended claims 15 and 16 find support in the application as filed.

Accordingly, it is respectfully requested that the Examiner reconsider and withdraw the new matter rejection of claims 1, 2, 4-13, and 15-25.

**Rejection under 35 U.S.C. §112, Second Paragraph – Indefiniteness**

Claims 1, 2, 4-13, 15<sup>2</sup>-25 stand rejected for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. The Examiner states that claim 1, and by dependence claims 2, 4-13, 15-25, are vague and indefinite because the following phrases in claim 1 are not clear: 1) “wherein the DNA sequence is upstream on the 5' side of the gene and 2) “the method comprising a step of controlling of transcription of the gene induces homologous combination.”

As discussed in the foregoing comments, claim 1 has been amended to clarify above-referenced phrase 2) that has been rejected. Specifically, amended claim 1 recites that homologous recombination is induced by controlling transcription of the gene using a transcription promoter that is located 3' of the DNA sequence; and the gene is located 3' of the transcription promoter.

With respect to the rejection of phrase 1) in amended claim 1, the Examiner states that it is not clear from phrase 1) whether the DNA sequence is being introduced into the cell or whether it is present in the genome. The rejection is traversed, and reconsideration is respectfully requested.

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<sup>2</sup> Applicants point out that the Examiner has incorrectly stated that claims 15 and 16 depend from claim 1. Instead, claim 15 is an independent claim and claim 16 depends from claim 15.

While this phrase has been deleted from amended claim 1, as discussed in the foregoing comments, Applicants direct the Examiner's attention, for example, to [0020] – [0025] of the '678 Publication. It is clear from a reading of these paragraphs that the DNA sequence, as required by the amended claims, can be artificially introduced into a genome (*i.e.*, exogenous) or can be naturally and originally present in the genome (*i.e.*, endogenous). Thus, the meaning of DNA sequence in amended claim 1 is clear.

Accordingly, it is respectfully requested that the Examiner reconsider and withdraw this rejection of claim 1, and claims 2, 4-13, and 17-25 that depend from claim 1.

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Additionally, the Examiner states that in claim 4 the phrase “the controlling transcription involves a cis-acting region comprising an enhancer a nuclear matrix attachment region (MAR) or both” is vague and indefinite.

As discussed in the foregoing comments, claim 4 has been amended to clarify the phrase that has been rejected. Specifically, amended claim 4 now specifies that the gene of the method is under transcriptional control by a cis-acting region. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw this rejection.

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The Examiner also states that in claim 6 the phrase “the enhancer or the nuclear matrix attachment region (MAR) or both” is vague and indefinite.

As discussed in the foregoing comments, claim 6 has been amended to clarify the phrase that has been rejected. Specifically, amended claim 6 recites that the vector further comprises an enhancer or a nuclear matrix attachment region (MAR), or both. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw this rejection.

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With respect to independent claim 15, and claim 16 that depends from it, the Examiner has not provided any reasons why these claims are indefinite. It is assumed that the reason is the same as for claim 1 since, as Applicants have pointed out in the foregoing comments, the Examiner has incorrectly stated that claim 15 depends from claim 1. As discussed in the foregoing comments, claim 15 has been amended to clarify that on the vector the DNA sequence, the promoter, and the gene are arranged in an order beginning with the DNA sequence, the transcription promoter 3' end to the DNA sequence, and the gene 3' to the transcription promoter. For at least these reasons, amended claim 15 is definite and clear. Claim 16 depends from claim 15, and specifies in the vector the location of the enhancer and the nuclear matrix attachment region relative to the location of the gene. Thus, the meaning of amended claim 16 is also clear.

As discussed in the foregoing comments, claims 1, 2, 4-13, and 15-25 are not indefinite. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw the indefiniteness rejections of these claims.

**Rejection under 35 U.S.C. § 102(b) – Anticipation**

Claims 1, 12, 13, 15, 17 stand rejected as being anticipated by Nickoloff et al. (*Mol. Cell. Biol.*, 12, 5311-5318, 1992) (hereinafter "Nickoloff"). According to the Examiner, Nickoloff discloses "a method for inducing homologous recombination of mammalian cells, wherein the efficiency of the homologous recombination of a neo gene for example, which has been embedded in the chromosome of a mammalian cell such as a CHO cell, and regulated by a DEX reactive MMTV promoter, and a different neo gene or the like is enhanced by activating transcription from the aforementioned DEX-reactive MMTV promoter." The Examiner also states "that the DNA sequence would be upstream or 5' of the gene with which recombination takes place, and promoter is 3' to the DNA sequence." Lastly, the Examiner contends that Nickoloff discloses vectors comprising said gene and sequence. *See*, March 6, 2009 Office Action, p. 4.

The rejection is traversed, and reconsideration is respectfully requested.

Anticipation requires that each and every element of the rejected claim(s) be disclosed in a single prior art reference. See MPEP § 2131 (8th Ed., Rev. 6, Sept. 2007). “A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

Amended claims 1 and 15 require a transcription promoter, for controlling the transcription of a gene, that is located in between the gene and the DNA sequence. Specifically, amended claim 1 recites that homologous recombination is induced by controlling transcription of the gene using a transcription promoter that is located 3' to the DNA sequence and that the gene is located 3' to the transcription promoter. Amended claim 15 specifies that on the vector the DNA sequence, the promoter, and the gene are arranged in an order beginning with the DNA sequence, the transcription promoter 3' to the DNA sequence, and the gene 3' to the transcription promoter. Thus, amended claims 1 and 15 are not anticipated because Nickoloff does not disclose the above-described positional relationship between a DNA sequence, a transcriptional promoter, and a gene. In contrast, Nickoloff describes in Figures 1 and 5 that on a vector, for example, a MMTV transcription promoter, a *neo'* DNA sequence, and a *neo* gene are arranged in an order beginning with the MMTV transcription promoter, the *neo'* DNA sequence 3' to the MMTV transcription promoter, and the *neo* gene 3' to the *neo'* DNA sequence. Thus, amended claims 1 and 15 are not anticipated by Nickoloff.

Since claims 12, 13, and 17 depend from amended claim 1, claims 12, 13, and 17 are also not anticipated by Nickoloff for at least the reasons discussed above with respect to amended claim 1. Additionally, claim 13, which is directed to a recombinant gene produced by homologous recombination induced according to the method of claim 1, is not anticipated by Nickoloff because the gene that is produced depends upon the claimed positional relationship of the DNA sequence, the promoter, and the gene in the method of inducing homologous recombination, which, as discussed in the foregoing comments, is not the same as Nickoloff. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw this anticipation rejection.

**CONCLUSION**


In view of the above amendments and remarks, it is believed that the claims are in condition for allowance and it is respectfully requested that the case be passed to issue.

Applicants reserve the right to pursue the cancelled and/or non-elected subject matter in one or more continuation or divisional applications.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: June 8, 2009

Respectfully submitted,

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